Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Formulation, Development & Characterization of Gels of Extracts of Butea monosperma & Acacia arabica Linn. & Evaluation of Wound healing Activity

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Cite this paper as: Dinesh Shakya , Namrata Singh , (2025) Formulation, Development & Characterization of Gels of Extracts of Butea monosperma & Acacia arabica Linn. & Evaluation of Wound healing Activity. *Journal of Neonatal Surgery*, 14 (32s), 6438-6445.

ABSTRACT

The extracts were tested for acute oral and dermal toxicity studies on the basis of OECD guidelines. Normal healthy albino rats were chooses and grouped for the wound healing study. The excision, incision and dead space wounds were implicated on back side of albino rats. In excision wound model extracts were applied topically for 14 days. At the end of study Wound area, % wound closure and day of epitheliazation were calculated.

In incision wound model all extracts were administered orally at a dose of 200 mg/kg body weight for 14 days. At the end of study tensile strength (Skin breaking strength) was measured with the help of tensiometer.

In Dead Space wound model all extracts were administered orally at a dose of 200 mg/kg body weight for 14 days. At the end of treatment the wet and dry weight of granulation tissue, hydroxyproline content with % collagen and % elastin level were measured. Some antioxidant parameters like SOD, GSH, and Catalase and lipid per oxidation level also estimated in blood of rats of dead space wound model. Among all extracts ethanolic extract of bark of Acacia arabica and Butea monosperma were found to be most effective in management of delayed wound healing.

The acute (Oral and Dermal) toxicity studies, excision, incision and dead space wound model were implicated for wound healing activity of ethanolic extract of Acacia arabica and Butea monosperma with all biophysical and biochemical parameter estimation same described above for examination of extract.

On the basis of above investigations, it is concluded that the ethanolic extract of bark of Acacia arabica and Butea monosperma have effective role in treatment of delayed wound healing in normal albino rats

Keywords: *Formulation, Development, Characterization of Gels, Extracts, Butea monosperma & Acacia arabica Linn, Wound healing Activity*

1. INTRODUCTION

Transdermal medication transport mechanism which includes all topically applied drug preparations intended to deliver the active ingredients into the systemic circulation (Latheeshjlal et al., 2011; Chittodiya et al., 2013). The skin is major organ of the human body and it is found at some places thin and at some places thick. The average thickness is about 1 to 2 mm. The skin comprises two layers i.e outer epidermis and inner dermis (Patil et al., 2019). Development of oral medication distribution is most common dosage delivery in the pharmaceutical field for patient compliance. In this drug administration method patient acceptance is advantageous but has significant drawbacks viz first pass metabolism, degradation of active pharmaceutical ingredient in gastrointestinal tract due to enzymes, pH of the stomach etc. Hence, defeat these drawbacks a Novel medication transport mechanism was developed. The use of gels has been increased in the pharmaceutical and cosmetics preparations. A gel is 99% weight liquid and colloid in nature immobilized by its surface tension and gelating agent forms a macromolecular arrangement of fibers (Verma et al., 2013; Saroha et al., 2013). The rigidity of gel is achieved by the gelling agent because particles interlocked and formed a network. The type of form and mature of particles which are responsible for the formation of linkages determine the composition of network and property of gel. When gel is applied on to the skin, the liquid evaporates and entrapped drug leaves in form of thin-film of gel-forming matrix which covers the skin (Verma et al., 2013). In our previous study, we have evaluated the different extracts of Butea monosperma Linn. And Acacia arabica Linn. In different models of wound healing and the effect of some potent extracts was observed. The aim of the.

present study was to develop one gel formulation of selected extracts and characterize them on the basis of different parameters (Wester et al., 1991)

2. MATERIAL & METHODS

2.1. Plant Materials Collections

As per facts, references received from literature survey, the bark of *Acacia arabica* were purchased from local market and bark of *Butea monosperma* were collected from local area for investigational study.

2.2. Shading, drying and grinding:

The bark of *Acacia arabica* and bark of *Butea monosperma* dried under shade for 15 days. The dried bark was grinded under mechanical grinder machine to prepare cores powder, for extractions.

2.3. Extraction of plant materials

The dried bark of *Acacia arabica* and bark of *Butea monosperma* were extracted by successive solvent extraction method with the help of soxhlet apparatus. The plant material first extracted with petroleum ether, chloroform, ethanol and water.

2.4. Determination of percentage yield

The percentage yield of extract was calculated by using following formula: -

Weight of Extract

Percentage yield = --- x 100

Weight of powder drug Taken

2.5. Formulation of topical gel

The United State Pharmacopeia (USP) defines gels as semisolid, being either suspensions of small inorganic particles or large organic molecules interpenetrated with liquid. In the first case, the organic particles, such as bentonites, from a three-dimensional "house of card" structure throughout the gel. This is a true two-phase system, as the inorganic particles are not soluble but merely dispersed through the continuous phase. Gels formulations of different concentration using different base were formulated the various ingredients used for the formulations. By using the above ingredients three different formulations were prepared. All formulations were having Carbopol gel base (Wysowski *et al*., 2002). Formulations I, II, were 1% of each concentration of extract and formulation III was 2% concentration (i.e. 1% of each extract). The concentration of extract of plant *Acacia arabica* & *Butea monosperma* were used on trial and error basis and studying its activity (Yeo *et al*., 2017).

Table 1: Formulation of topical gel

Name of Ingredient	Formulation I	Formulation II	Formulation III
Carbopol 940	1gm	1gm	1gm
Glycerin	5ml	5ml	5ml
Tri -ethanolamine	q.s.	q.s.	q.s.
Propyl paraben	q.s.	q.s.	q.s.
Acacia arabica	1gm	-------	1gm
Butea monosperma	-------	1gm	1gm
Distilled water q. s.	100ml	100ml	100ml

2.6. Characterization of Polyherbal Gel

Vesicle size, Particle size distribution and zeta potential (ZP)

Using various microscope imaging techniques, the generated vesicular formulations were characterized for morphological properties such as vesicle shape, lamellarity, surface morphology, and aggregation. Prior to sonication, the creation of vesicular structure and shape of the produced vesicles was examined using an optical microscope (Labomed inverted

microscope, TCM 400, USA). A drop of diluted vesicular suspension was kept on a clear microscope slide, spread uniformly by putting the cover slip, and viewed under a 10 X magnification optical microscope (Yilmaz *et al*., 2019). *Acacia arabica* & *Butea monosperma* morphology SEM was used to examine gel. Under scanning SEM, the surface morphology of the produced examined (JEOL, JSM-6360, Japan). A drop of the vesicular formulation was homogeneously put to a clean glass slide and allowed to air dry. The sample was gold coated with a Sputter coater (JEOL, Japan) and examined under SEM with a 20kV accelerating voltage. One drop of the diluted formulation was evenly spread out on a clean glass piece and left to air dry overnight (Zu *et al*., 2010).

2.7. Entrapment Efficiency

Aliquots of optimized gel 2gm were subjected to centrifugation using a cooling centrifuge at 11,000 rpm for 90 minutes. The clear supernatant was separated from pellet.

The pellet was dried in a vacuum oven. Accurately weighed 25 mg of the pellet was dissolved in 10ml of methanol and sonicated for 20-30 min to lyse the gel and then diluted with phosphate buffer saline (PBS) (pH 7.4) The solution was suitably diluted and absorbance measured at λmax 226 nm and 265 nm (Tran *et al*., 2019). The per cent entrapment was calculated using the formula,

% entrapment = amount of *Acacia arabica* & *Butea monosperma* in sediment/amount of added X100.

Entrapment efficiency (% EE) was determined as follows: EE % = (T−S)/T x 100

2.8. Viscosity

The viscosity of manufactured gels was measured using an LV Brookfield, DV-E viscometer with spindle no 64 at rpm 100 and recorded at a regulated temperature of 252°C (in cps).

2.9. Spreadability

After 1 minute, the spreading diameter of 1 g of gel between two horizontal plates (20 cm 20 cm) was measured to determine the spreadability of the gel formulation. The upper plate was given a standard weight of 125 g. (Tiwari *et al*., 2018).

2.10. pH measurement

The pH of the gels was measured with a pH pocket-sized digital pH meter.

2.11. Drug content

In order to achieve total solubility of the formulation, gels were dissolved in 100ml of PH 6.8 or pH 7.4 Phosphate buffer solution (PBS) and agitated for 2 hours on a mechanical shaker. After passing the solution through the filter paper, 100 litres of the filtrate were extracted. The filtrate was diluted with 3.5 mL distilled water, and the drug content was determined using a UV-Visible spectrophotometer set to max 257nm and a 6.8 or pH 7.4 Phosphate buffer as a blank (Thielitz *et al*., 2001).

***2.12. In-Vitro* Drug Release Study Using Franz Diffusion Apparatus**

In-vitro absorption studies are generally carried out in vertical Franz diffusion cell. The vertical Franz diffusion cell is commonly used for in-vitro absorption research. It is an appropriate instrument for quality control of topical medicines, according to Food and Drug Administration (FDA) requirements. It has a donor chamber and a receptor chamber that are both filled with phosphate buffer media.

Various kinetic models were used to characterize the release kinetics in the in-vitro data. The zero order rate characterizes situations in which the rate of drug release is unaffected by its concentration. The first order describes the release from a system where the rate of release is proportional to the concentration. Higuchi (1963) defined drug release from insoluble matrix as a time-dependent square root process based on Fickian diffusion. The results of *in-vitro* release profile obtained for all the formulations were plotted in models of data treatment as follows (Thiboutot DM., 2001):

2.13. Zero order kinetics:

Zero order release would be predicted by the following equation:

$At=A_0 – K_0t$

2.14. First order kinetics:

First order kinetics could be predicted by the following equation:

$Log\ C= \log C_0-K_t / 2.303$

Where,

C= Amount of drug remained at time ‗t'.

C_0= Initial amount of drug.

K= First order rate constant (hr^{-1})

When the data plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant ‗K_t' can be obtained by multiplying 2.303 with the slope value.

2.15. Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following

Higuchi's classical diffusion equation:

$Q= [DЄ/\tau(2A-ЄC_S) C_St]1/2$

Where,

Q= Amount of drug release at time ‗t'.

D= Diffusion coefficient of the drug in the matrix. A= Total amount of drug in unit volume of matrix. C_S = Solubility of drug in matrix.

Є= Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs at which q amount of drug is released).

When the data is spited according to the equation i.e., cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism (Higuchi's 1963).

2.16. Korsmeyer equation/ Peppa's model:

To study the mechanism of drug release from the liposomal solution, the release data was also fitted to the well-known exponential equation (Korsmeyer equation/ Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$Mt/ M\alpha = Ktn$

2.17. Wound Healing Activity of Polyherbal Gel

Excision wound model in albino rats

Excision wounds were used for the study of rate of contraction of wound and epithelization; all wounds were of full-thickness type extending up to the adipose tissue. Animals were anaesthetized with slight vapour inhalation of di-ethyl ether and the back side of each rat was shaved. Excision wounds sized 300 mm^2 and 2 mm depth were made by cutting out piece of skin from the shaven area. The entire wound was left open. Animals were closely observed for any infection and those which showed any sign of infection were separated, excluded from study and replaced. The treatment was done topically in all the groups. The extract of both plants were applied at a dose of 200 and 400 mg/kg/day for 15 days. Wound areas were measured on days 1, 4, 8 and 15 for all groups, using a transparency sheet and a permanent marker. Recording of wound areas were measured on graph paper.The day of scar falling, after wounding without any residual raw wound was considered as the day of epitheliazation. The groups were prepared as follows and each group contains 6 rats (Sahoo *et al*., 2013).

Group I: Control group.

Group II: Test group treated with *Acacia arabica* 1% gel. (Formulation I)

Group III: Test group treated with *Butea monosperma* 1% gel. (Formulation II)

Group IV: Test group treated with (Polyherbal 1% gel) (Formulation III)

Group V: Reference Standard Marketed Preparation (Povidone Ointment).

2.18. Statistical analysis

The data were expressed as mean ± SEM. The data were analyzed by one way analysis of variance (ANOVA) followed by "Dunnett's test"; p value less than 0.05 was considered as statistically significant with the help of Graph pad Prism 5.04 trial version.

3. RESULTS & DISCUSSION

3.1. Characterization of gel

Physical Appearance, Consistency, pH and Drug Content

Gel formulations prepared and evaluated after 24 hours for its physical appearance, consistency, pH, drug content. All were observed as transparent, opaque, viscous gel, Flowable characteristics and exhibits uniform appearance. Formulated Gel observed with pH in the range of 5.0 to 5.7 which can be considered good enough to circumvent the risk of irritation which occurs by application onto the dermal layer because the pH of the skin is between 5.4 – 5.9.The drug content observed between 98.16% to 103.87% for all Gel preparations (Ramya *et al*., 2013). Hence, it might implicit with goal of the prepared Gel suitable for application with the skin. The outcomes of physical appearance, consistency, pH and drug content were depicted table.

Table 2: Observation of Physical Appearance, Consistency, pH and Drug Content

Formulation	Appearance	Consistency	pH	Drug Content
1	Transparent	Flowable	5.2 ± 0.11	99.30
2	Transparent	Gel	5.3 ± 0.11	97.85
3	Opaque	Flowable	5.3 ± 0.12	98.41
4	Opaque	Gel	5.4 ± 0.12	100.23
5	Transparent	Flowable	5.3 ± 0.06	102.05
6	Transparent	Gel	5.6 ± 0.13	99.11

3.2. Viscosity

Viscosity is an important rheological parameter of the Gel, which plays an imperative function in administration & preparation of Gel preparations. Viscosity associated with physical and mechanical properties for example hardness, consistency, spreadability of gel preparation successively related to easiness of removal of gel through the container, effortlessness of use at site of application and experience of formulation. Apparent viscosities of prepared Gel formulations had determined by using rotational viscometer by means of 'T' shaped spindle exert least disturbance to the sample, at the shear rate of 10 rpm (Pereira *et al*., 2016).

Suggested design point exhibits a shear-thinning action when rate of shear increases viscosity decreases. This is an enviable property in gel formulation because it must be thin whenever it is used. It is assumed that, pseudoplastic flow of Gel may because of progressive split of inner arrangement of preparations and re-enactment through Brownian movement (Patel *et al*., 2018).The viscosity measured at shear rate of 10 rpm are given in table.

Table 3: Viscosity of the Gel Formulation

Formulation	Speed of spindle (rpm)												
	0.4	0.6	0.8	1	1.5	2	2.5	3	4	5	6	10	12
1	65500	54300	40200	32600	28300	23400	20500	18300	15600	12700	10300	9000	7850
2	1280000	885000	758000	556000	465000	385000	342500	296000	275800	265000	236000	215600	210000
3	156500	122600	105000	85400	69300	57400	45300	38600	32400	27500	22300	18500	16500
4	3805000	2420000	1950000	1350000	1005000	805000	701200	656000	500600	495000	425200	335000	285000
5	91500	70500	62300	55000	48000	42500	38300	32800	28200	24500	21900	17000	15300
6	1935000	1410000	1180000	785000	625000	510250	410250	350200	325000	295600	255500	205200	195000

Semisolid preparations applied topically mostly have viscosity of 250000 – 1000000 cps for its easy application and withholding. Formulations 1, 3, 5 and 6 shows less than 200000 cps viscosity at nominal shear rate and formulation shows the slightest resistance to flow shows.

3.3. Spreadability

Good spreadability is one of an essential criterion of Gel. It is an imperative feature in topical application and revealed straightforwardness of therapy. An effectiveness of gel remedy determined on spreadability on smooth stratum of the skin which distributes proper dose. Optimal uniformity of similar preparation help to make sure an appropriate dose is delivered to an application site. This is predominantly vital in the midst of potent drug preparation. Minimized concentration of drug will not deal out the most wanted outcome whereas side effects observed when too much drug concentration delivery at application site. Spreadability governs the release of accurate drug dose from gel formulation.

An essential aspect to think about, while evaluation of spreadability of a preparation, which includes the temperature of the application location, rate and time of shear formed upon smearing. Most commonly preferred method to quantify and determine the spreadability of gel formulation is parallel plate method. It provides reproducibility, accuracy and statistically significant information. Ease and comparative lack of expenditure are benefits of this technique. The data generated by this method should be presented and interpreted manually.

The result of spreadability found 121 gm.cm/min for formulation 6 and 498 gm.cm/min for emulgel preparations 9. Every value is presented as average of three readings. Preparations with less concentration of Ulterz 10 i.e. 1, 3, 5, 7 and 9 shows highest spreadability index.When Ultrez 10 concentration augmented as of 1.25% to 4.50% by maintaining constant concentration of surfactant at 37.5% and oil concentration at 7.5% shows enormously noteworthy fall in spreadability. It might because of the effect of physical characteristics and concentration of polymer used in the formulation of Gel.

3.4. Residence Time (RT):

The poor spreadability observed with highly viscous gel which possesses excellent residence time on application site. Action of drug will be prolonged because of long residence time at site of application. Polymers Ultrez 10 has good adhesion property and hence can be use in gel formulations.

Formulation 6 shows maximum RT of 30.67 ± 0.87 min, formulations 4, 10 and 12 shows > 15 min. Formulation 1, 5 exhibits less than 1 min. As Ultrez 10 concentration increases from 1.25 % to 4.5 % residence time improved drastically. This will able to explain by amplify of concentration of polymer chain length present in favor of diffusion in to agar film. Too less concentration of polymer, amount of incisive polymer chains for each part of agar volume is little and polymer interaction. Hence extra polymer concentration results in lengthy incisive chain measurement lengthwise and improved stability on the skin.

In addition to adhesion property, superior viscosity also increases the residence time of preparations. As the concentration of oil increases by keeping constant the other ingredients, results in increased viscosity of formulations and finally increase in the residence time significantly except for formulation 6, possibly because of the interaction of other factors.

3.5. Extrudability:

The extrusion of the Gel from the tube is an important during its application and in patient acceptance. Emulgel with high consistency may not extrude from tube whereas, low viscous gels may flow quickly and hence suitable consistency is required in order to extrude the Gel from the tube. Extrudability of prepared formulations was found to be good.

Table 3: Spreadability, Residence Time and Extrudability of Gel Formulations

Formulation	Spreadability (gm.cm/min)	RT (minute)	Extrudability (g)
1)	425.8 ± 4.13	0.61 ± 0.06	0.88 ± 0.06
2)	217.4 ± 3.39	8.09 ± 0.98	0.96 ± 0.04
3)	355.5 ± 3.07	5.21 ± 0.23	1.08 ± 0.13
4)	189.4 ± 2.49	25.78 ± 0.19	0.95 ± 0.03
5)	410.8 ± 3.05	0.56 ± 0.07	1.19 ± 0.09
6)	221.7 ± 3.41	3.10 ± 0.16	0.08

3.5. In Vitro Drug Release

The viscosity might govern release of medication from an Gel. As the viscosity of gel increases, drug's release may be slows. Release of Gel at initial stage is pretentious by amount of gelling agent in almost all formulations. Formulation contains 4.5% or above concentration of Ulterz 10 i.e. Formulation-2, Formulation-4, Formulation-6 seems to retain the drug apart from proportion of oil to surfactant.Whereas, formulations 5 and 6 releases more than 95% of Gel.

It was observed that varied concentration of surfactant showed significant difference in release of drug in dissolution medium. This outcome might result from an ability of agent which lowers interfacial tension among aqueous along with oily phase of dispersion by escalating hydrophilicity so-that increases ingress of dissolution medium in Gel arrangement and hence increases drug release. When the concentration of oil phase increased from 7.5% to 20% it was observed that decrease in drug release. This effect might be escaping tendency of drug.

Table 4: % Drug Release of Gel Formulations

Formulation	Release of Drug	
	1st hour (%)	8th hour (%)
1	85.23 ± 2.21	90.05 ± 2.63
2	9.77 ± 1.55	42.69 ± 1.57
3	12.33 ± 1.15	35.87 ± 0.48
4	0.00	1.09 ± 0.91
5	92.45 ± 2.47	101.03 ± 2.13
6	4.56 ± 1.18	75.23 ± 3.35

4. CONCLUSION

The herbal formulations made by above said extracts could be more beneficial for society, and further study related with isolation of potent chemical compounds and responsible biological quantitative confirmation from bark of *Acacia arabica* and *Butea monosperma* could meet in the form of treatment for physical or chemical injury complications especially for wound healing complications in patients

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